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10/518,575	08/04/2005	Salah-Dine Chibout	DC4-32567A	7721

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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,575	CHIBOUT ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,9,10,12,15,21,22,29,30 and 37-60* is/are pending in the application.

4a) Of the above claim(s) *3,4,12,15,21,22,29,30 and 37-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed 8/8/2008.

The amendment to the specification has brought the specification into sequence compliance.

Claims 2, 5-8, 11, 13-14, 16-20, 23-28 and 31-36 have been canceled.

Claims 1, 3-4, 9-10, 12, 15, 21-22, 29-30, 37-60 are pending.

Claims 3-4, 12, 15, 21-22, 29-30 and 37-60 have been withdrawn from consideration.

Claims 1, 9 and 10 are being examined.

The written description rejection has been withdrawn in view of the amendment.

The previous objection to the claims has been overcome in view of the amendment.

The 102 based on Kang has been withdrawn as claim 13 has been canceled.

Claim Rejections - 35 USC § 112

Enablement

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 9, and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection has been maintained but modified to reflect amendments to the claims.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to a method of determining renal toxicity in "any" individual by obtaining "any" bodily sample from a subject to whom a compound suspected of causing renal toxicity has been administered, determining gene expression of KIM-1 and clusterin to determine a first set value wherein expression of Kim1 is measured as the mRNA in the bodily sample that binds a probe comprsing the

sequence of SEQ ID NO 3 and the gene expression of clusterin is measured as the mRNA in the body sample that binds a probe comprising SEQ ID NO 15, comparing the first set value with a second value from an individual not subject to whom the suspected renal toxicity compound has not been administered wherein the first value being greater than the second value for KIM-1 and clusterin, indicating the individual is having developing or is sensitive to renal toxicity.

The claims thus are broadly drawn to the "any" individual which include dog, cats, apes, rats, etc.

The claims are broadly drawn to analysis of gene expression in "any" bodily sample.

The claims are broadly drawn to determining renal toxicity based on any sequences that hybridize to any portion of SEQ ID NO 3 and SEQ ID NO 15.

The claims are further broadly drawn to determination of renal toxicity by administration of "any" dose of a compound suspected of causing renal toxicity.

Further the claims do not set forth how or if the samples are to be normalized so the expression data comprise raw as well as normalized data.

Further the claims are drawn to "any" type of renal toxicity caused by any compound.

Dependent claims draws the absolute mRNA expression level to KIM-1 to above 1.5 E+07 and clusterin above 1.90E+09 or a 20 fold overexpression of Kim 1 and at lest a 7 fold overexpression of clusterin.

Dependent claim 10 draws the method to a 20 fold induction of for KIM-1 and at least 7 fold for clusterin is an indication that the individual is having or developing renal toxicity.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches in Table 1 sequences for KIM-1 are available by Genbank accession AF035963, AL159977, AC073225.5, AC025449.6, AF165926, AL449103, AI662116.

The specification teaches in Table 1 sequences for clusterin are available by Genbank accession U02391, M64723, M64723, J02908, L00974, M25915, M63379, M64722, M74816, X14723, AF182509, D14077, L05670, L08235, S70244.

The specification teaches in experiment 1 treatment of rats with cyclosporin A and isolation of RNA from the kidneys and analysis by probe arrays (see page 35). The specification does not teach which array was used and thus does not teach which genes were present on the array to normalize expression between samples.

The specification further teaches that serum clusterin levels were increased in animals treated with nephrotoxic compounds (see table 3). However, the specification does not teach this increase is statistically significant.

The specification further teaches that real time PCR analysis demonstrated that as pathology grade of rat kidney failure increased so did the expression in the kidney of clusterin and Kim-1 relative to B-actin levels (see figure 1).

The specification further teaches in experiment 2, a study of rats treated with test compound 1 (TC1) in cyclosporine A at 20 mg/kg/day, 60 mg/kg/day for 14 days , or in cyclosporine A at 10 mg/kg/day, 25 mg/kg/day for 25 days a control microemulsion (see page 37, lines 17-25). The specification teaches these genes were analyzed by PCR and the data is represented in Figure 3. Figure 3 appears to suggest that TC1 was administered alone with the emulsion. Figure 3 further teaches that the TC1 resulted in between a 1 and 10 fold increase Kim-1 expression in male and female rats at doses examined. However, TC-1 resulted in decreased expression of clusterin in males rats at all doses and with females at 60 mg/kg/day. Further figure 3 teaches that 20 mg/kg of cyclosporine A increases KIM-1 expression approximately 90 fold, and clusterin expression approximately 3 fold. The specification asserts on page 38 that this data confirms the validity of prediction based on these marker genes. The specification does not present any data as to the kidney status of any groups; so that one could form a nexus that increased KIM-1 and clusterin expression are correlated with renal toxicity.

The specification teaches experiment 4 in which male rats were treated with 5 or 20 mg/kg/day of cyclosporine A and compared to controls (see page 39, lines 5-10). The specification does not teach if the controls were treated with the cyclosporine A carrier, or not treated at all. The specification further teaches RNA was isolated from kidneys and analyzed by Affymetrix RU34A rat gene chips (see page 39, line 20). The specification teaches, "For the genes listed in Table 6, the overall differences among the different treatment groups were statistically significant ($p<0.001$)" see page 39, lines 25-26). The specification teaches in Table 6 that KIM-1 expression has a control value of

6.5 in 16 control rats, 5.9 in 4 rats treated with 5 mg/kg/day of cyclosporine A, and 168 in 7 rats treated with 20 mg/kg/day of cyclosporine A. The specification teaches in Table 6 that clusterin expression has a control value of 305 in 16 control rats, 302 in 4 rats treated with 5 mg/kg/day of cyclosporine A, and 2309 in 7 rats treated with 20 mg/kg/day of cyclosporine A. It is unclear how there is a statistical difference in the expression of KIM-1 and clusterin between the low dose and control groups as suggested by the teachings of the specification.

The specification appears to contradict the teachings of page 39, lines 25-26 on page 41 where it states, " As shown in Table 6, the expression of KIM-1 was induced 26-fold in rats treated with 20 mg/kg/day CsA as compared to the control rats ($p<0.001$). No induction of KIM-1 was detected in rats treated with 5 mg/kg/day CsA. The changes in KIM-1 expression by CsA (20 mg) compared to CsA (5 mg) are statistically significant ($p<0.004$)."

The specification appears to contradict the teachings of page 39, lines 25-26 on page 41 where it states, " The expression of Clusterin was induced 7.6-fold in rats treated with 20 mg/kg/day CsA as compared to the control rats (Table 6; $p<0.001$). No induction of Clusterin was detected in rats treated with 5 mg/kg/day CsA. The changes in Clusterin expression by CsA (5 mg) compared to CsA (20 mg) are statistically significant ($p<0.001$)."

However, the data of experiments 2 and 4 demonstrate great variability in the effect of 20 mg/kg/ day cyclosporine A on clusterin and KIM-1 expression, suggesting the fold increase in expression of these gene is not predictable. Further as experiment

2 clearly demonstrates that female and male rats respond differently to the same compounds it would be unpredictable to correlate findings in males with female rats.

Presence and absence of working examples

The specification does not teach any a method of detecting absolute levels of mRNA or mRNA in any tissues other than kidney.

The specification does not teach cyclosporine, cisplatin, tacrolimus, aminoglycosides, sulfonamides and trimethadione have a similar mode of action. Further the specification does not teach how these drugs cause renal toxicity, such that a nexus between the teachings of cyclosporine can be extrapolated in any other drug.

The state of prior art and the predictability or unpredictability of the art:

Vandesompele teaches, "Accurate normalization of gene expression levels is an absolute prerequisite for reliable results, especially when the biological significance of subtle gene expression differences is studied" (see page 9, 2nd column, discussion) (Vandesompele et al (Genome Biology (2002) volume 3 , pages 1-11). Vandesompele teaches, "That the conventional use of a single gene normalization leads to relatively large errors in a significant portion of samples tested" (see abstract, results). Vandesompele teaches that ACTB (beta actin) appears to be the one of the worst genes fro normalization and thus resulting in large normalization errors (see page 10, 1st paragraph). Vandesompele teaches at least 3 housekeeping genes are required for accurate normalization (see page 10, 1st column, 1st full paragraph). Vandesompele thus teaches that studies of gene expression using a single gene for normalization are

unpredictable due to the large variation in the expression of the genes used for normalization.

The art of Cheung et al (Nature Genetics, 2003, volume 33, pages 422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3).

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of Pathology, 2001, volume 195, pages 53-65). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The prior art of Newton et al (Journal of Computational Biology, 2001, volume 8, pages 37-52) further teaches the difficulty in applying gene expression results. Newton et al teaches

that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph).

Perazella et al (Expert Opinion on Drug Safety, 2005, Volume 4, pages 689-706) teaches the mechanism of drug toxicity can vary greatly with pharmacological action, metabolism and ultimate pathway of excretion of agent administered (see page 689, 1st paragraph after abstract). Perazella et al teaches that cyclosporine and tacrolimus are associated with prerenal azotemia, renal vascular disease, but not glomuler disease, interstitial nephritis, acute tubular necrosis, crystal nephropathy, or post-renal azotemia (see boxes 1-8). Perazella further teaches the cisplatin is associated with vascular kidney disease, interstitial nephritis, acute tubular necrosis, crystal nephropathy, postrenal azotemia (see boxes 1-8). Perazella further teaches the aminogylcosides are associated with acute tubular necrosis (see boxes 1-8). Thus Perazella teaches the recited cytotoxic drugs have different modes of action and affect the kidney differently. Due to Perazella's teachings it would be unpredictable to associate the different drugs recited with the same renal toxicity as each has a different with pharmacological action, metabolism and ultimate pathway of excretion of agent administered.

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed the skilled artisan would first have to determine which if detection of an increase in "any" mRNA that hybridizes to SEQ ID NO 3 and "any" mRNA hybridizes to SEQ ID NO 15 relative in a sample taken from a subject treated with a compound suspected of causing renal toxicity relative to a subject not treated with the compound is indicative that the individual is having or developing renal toxicity. It would be unpredictable to associate increased expression of any mRNA that bind to SEQ ID NO 3 and SEQ ID NO 15 under any conditions as this broadly encompasses the binding of the mRNA to any portion of the probes of SEQ ID NO 3 and SEQ ID NO 15. The specification nor art provide no nexus for a correlation of any mRNA that binds to any portion of SEQ ID NO 3 or SEQ ID NO 15 and the determination of renal toxicity.

Further the skilled artisan would have to determine what level of increased expression of clusterin and KIM-1 mRNA is required to determine renal toxicity. Wu, Cheung, Newton and Greenbuam teach that gene expression is variable across individuals and normalization is critical for predictability. Further Vandesompele teaches that at least 3 controls are required for accurate normalization and thus predictable results. As the specification teaches a single experiment in which normalization is described to a single gene (b-actin experiment 1), it would be unpredictable to associate these results due to the teachings of Vandesompele, Wu, Cheung, Newton and Greenbaum. Further the experiments have not been replicated, as experiment 2 and 4 merely confirm the expression data with cyclosporine treatment, but do not renal toxicity was examined directly. It would thus unpredictable.

The claims requiring specific levels or overexpression or absolute mRNA levels would further be unpredictable, due to the normalization issue described above. Due to the normalization issues one of skill in the art would not be able to adequately determine the fold alteration in expression without knowing the controls by which to normalize expression to and the art clearly teaches the control used is critical. Further the claims drawn to absolute mRNA levels are unpredictable as the specification does not teach these levels or how to obtain these levels and the art teaches that mRNA is variable across species. Further the specification does not teach how to determine absolute mRNA values. Thus it would be unpredictable to use absolute mRNA levels with renal toxicity.

Further it would be unpredictable to associate a specific fold increase in expression of clusterin and KIM-1 with renal toxicity as each experiment appears to teach a different level of increase and only experiment 4 gives the fold expression required in the claims and experiment 4 does not provide that renal toxicity occurs.

Further it would be unpredictable to extrapolate the data presented in the specification with respect to the effect of cyclosporine A to the cyclosporine, cisplatin, tacrolimus, aminoglycosides, sulfonamides and trimethadione as Perazella teaches these drugs have different pharmacological action, metabolism, and excretion. Perazella further teaches these compounds affect the kidney differently and thus have different effects. It would thus be unpredictable extrapolate the findings of a single compound to large classes of unrelated compounds without a nexus for extrapolation in the art or specification.

Further it would be unpredictable to associate findings in kidneys from male rats with kidneys in female rats as figure 3 clearly depicts that in rats there are differences based on the sex of the animals. Further the specification does not demonstrate that the studies in rat kidney's allow for predictable correlations in any other species or any other tissues.

The specification and claims do not adequately describe the normalization controls used such that the skilled artisan would know how to make and use the instant invention, even in the described rat model.

Therefor, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

The response asserts the amended claims are enabled and the instant claims do not recite the method is a stand alone diagnostic.

These arguments have been thoroughly reviewed but are not considered persuasive. While the amendment has limited the instant claims to detection of sequences that bind SEQ ID NO 3 and SEQ ID NO 15, this encompasses an enormous number of mRNAs that are complementary to any portion of the SEQ ID NO. The specification nor art suggest an increase in "any" mRNAs that binds SEQ ID NO 3 or SEQID NO 15 are indicative of renal toxicity. Further neither the amendment to the

claims nor the response have addressed the issues as to the variability of gene expression as taught by Vandesompele, Wu, or Cheung in the Ofiice action of 12/18/2007. Thus it would be unpredictable to make comparison between groups due to the known variability in gene and expression and lack of guidance to normalization as suggested in the first action.

Further the amendment to the claims has in the preamble to claim 1 drawn the claims to treatment of an individual with "any" compound at "any" dose suspected of causing renal toxicity in comparison to an individual that has not been treated with the compound. It would be unpredictable to associate any dose of any drug with renal toxicity as figure 3 clearly demonstrates that different doses of a drug have a different response. Further, figure 3 teaches that there are differences to the expression of rat KIM-1 and Clusterin between male and female rats at different doses. Finally figure 3 of the instant specification teaches that clusterin expression is not predictably associated with increased expression of clusterin in male or female rats treated with cyclosporine as males treated with 20mg/kg, males treated with 60mg/kg had decreased expression. Thus it would be unpredictable to use the instant method for determination of renal toxicity either alone or in conjunction with other tests, as the expression of clusterin is not predictable increased by treatment of rats with cyclosporine, a drug known to caue renal toxicity.

Summary

No claims are allowed.

Conclusion

3. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Sarae Bausch/
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